## *Remarks*

### *I. Status of the Claims*

Upon the entry of the foregoing amendment, claims 2, 4-6, 9, 13-14, 20-22, 25, 79-80, 85, and 88-93 are pending in the application, with claim 85 being the independent claim. Claims 4-5, 13, 21-22, 25, 79, and 85 are herein amended. Claims 7-8, 16, and 23-24 are currently withdrawn. Claims 1, 3, 10-12, 15, 17-19, 26-78, 81-84, and 86-87 have been cancelled without prejudice or disclaimer of the subject matter therein. Applicants reserve the rights to pursue the cancelled subject matter in related applications. New dependent claims 88-93 have been added. Support for the amended and new claims is found in paragraphs [0139] through [0142] of the present application. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

### *II. Rejections under 35 U.S.C. § 112, Second Paragraph*

The Examiner rejected claim 74 under 35 U.S.C. § 112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter.

The Examiner contends that "[c]laim 74 recites the limitation 'system' in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Base claim 87 recites 'kit'." Office Action at page 2.

As set forth above, Applicants have cancelled claim 74, thereby rendering moot the Examiner's objection.

Withdrawal of this objection is respectfully requested.

***III. Rejections Under 35 U.S.C. § 103***

Claims 2-6, 9, 11, 20-22, 25, 27-31, 34, 36, 45-47, 50, 79, 81, 85, and 86 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 92/07952 A1 (hereinafter, "Rothbard") in view of US 2003/0191286 A1 (hereinafter, "Hildebrand"). By the foregoing amendments, claims 3, 11, 27-31, 34, 36, 45-47, 50, 81, and 86 have been cancelled. Hence, this rejection has been rendered moot as it may have applied to the cancelled claims. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki,* 745 F.2d 1468, 1471-73 (Fed. Cir. 1984). As set forth in *Graham v. John Deere Co. of Kansas City*,

> [u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined.
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> 383 U.S. 1, 17 (1966).

In addition, the Examiner must show reasons, explicit or otherwise, that would compel one of ordinary skill in the art to combine the references in order to make and use the claimed invention. To determine whether there is "an apparent reason to combine" the known elements in the way an application claims,

> it will be necessary. . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art. . . . To facilitate review, this analysis should be made explicit.

*Id.* at 14; *see also* Memorandum from the United States Patent and Trademark Office, "Supreme Court decision on *KSR Int'l. Co. v. Teleflex, Inc.*," (May 3, 2007) ("The Court did not totally reject the use of 'teaching, suggestion, motivation' as a factor in the obviousness analysis. . . . [I]n formulating a rejection . . . based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.").

Applicants assert that the cited references fail to disclose or suggest the claimed methods and provide no apparent reason to combine the references cited by the Examiner to arrive at the claimed invention. Applicants further assert that a person of ordinary skill in the art would have no reasonable expectation of success in making the claimed invention.

The pending claims are directed to a method for quantifying the exchange of a homogeneous template MHC-binding peptide with a first competitor peptide on an MHC complex, said method comprising:

a) incubating in a first reaction vessel under a liquid phase condition:

(i) a ternary complex comprising: at least one HLA-A2 monomer or at least one modified HLA-A2 monomer, the homogeneous template MHC-binding peptide, and beta-2 microglobulin, wherein the HLA-A2 monomer or modified HLA-A2 monomer maintains the ability to assemble into a ternary complex with the template MHC-binding peptide and beta-2 microglobulin;

(ii) an excess amount of a first competitor peptide; and

(iii) a tracer MHC-binding peptide tagged with a detectable label, wherein the tracer MHC-binding peptide competes with the first competitor peptide and the template

peptide for binding to the monomer, and wherein the template MHC-binding peptide has a lower affinity than the tracer MHC-binding peptide for the monomer;

b) incubating in a second reaction vessel, run parallel to the first reaction vessel, under liquid phase condition:

(i) the ternary complex; and

(ii) the tracer MHC-binding peptide tagged with a detectable label, wherein the tracer MHC-binding peptide displaces at least 90% of the template MHC-binding peptide; and

c) measuring a signal produced by:

(i) an MHC complex formed between the HLA-A2 monomer or modified HLA-A2 monomer, the tracer MHC-binding peptide, and beta-2 microglobulin in the presence of the first competitor peptide; and

(ii) an MHC complex formed between the HLA-A2 monomer or modified HLA-A2 monomer, the tracer MHC-binding peptide, and beta-2 microglobulin in the absence of the first competitor peptide; and

d) correlating the signals to quantify the exchange of the homogeneous template MHC-binding peptide with the first competitor peptide on the MHC complex.

Applicants assert that Rothbard, in combination with Hildebrand, does not disclose, suggest, or otherwise contemplate the method of the claimed invention. Rothbard discloses a first method in which MHC glycoproteins preloaded with either a heterogeneous mixture of endogenous peptides or a homogenous population of endogenous peptide is incubated with a detectable agonist (tracer peptide) in the presence of a competitor candidate moiety under conditions where the agonist is known to form a complex with the MHC glycoprotein. The

resulting complex is separated from the reaction mixture, and the effect of the candidate moiety on the agonist included in the complex is measured. *See* Rothbard at page 4, lines 1-9, page 5, lines 12-24, page 10, lines 8-19, and page 28, claim 15.

Rothbard discloses a second method in which the MHC monomer is first stripped off the template peptide by dilution and the "empty pocket" of the MHC monomer is then occupied by the incoming tracer or competitor peptide. *See* Rothbard at page 13, lines 30-34, and page 14, lines 20-21.

However, Rothbard does not disclose a method of the claimed invention of quantifying the exchange of a homogeneous template MHC-binding peptide with a first competitor peptide on an MHC complex.

The Examiner contends that while "WO 92/07952 A1 does not teach that the MHC molecule is HLA-A2", "[i]t would have been prima facie obvious to one of ordinary skill in the art to have used the soluble HLA-A2 monomers disclosed by US 2003/0191286 A1 as the MHC molecule in the method taught by WO 92/07952 A1." Office Action at pages 3 and 4. Applicants disagree with the Examiner's contention.

Applicants assert that while Hildebrand (US 2003/0191286 A1) discloses the use of soluble HLA-A2 monomers, the deficiencies of Rothbard, as discussed above, are not overcome by the disclosure of Hildebrand. The Examiner states that "US 2003/0191286 A1 discloses making MHC class I molecules, including HLA-A2, with or without endogenous peptides loaded therein, and further discloses representative HLA-A2 binding peptides of nine or ten amino acid residues in length." Office Action at page 3. However, as set forth above, Rothbard fails to disclose the method of the claimed invention. Therefore, Applicants

maintain that Hildebrand does not combine with Rothbard to disclose the method of the claimed invention.

The Examiner states "[w]ith regard to the limitation recited in instant claims 4 and 29 'wherein said liquid phase condition includes incubating the sample for about 2 to 20 hours,' the art reference discloses incubating 2 days or 48 hours, and so meets the claim limitation." Office Action at page 4.

The Examiner further contends that "[w]ith regard to the limitation recited in instant claims 5 and 30 'wherein said liquid phase condition further includes incubating the sample at about 21 degrees C,' the art reference discloses incubating at room temperature of 37 degrees C, and so meets the claim limitation." *Id.*

The Examiner also states that "[c]laims 2-6, 9, 11, 20-22 and 25 are included in this rejection because the art method of measuring affinity of a peptide of interest is also identifying said peptide for binding to MHC." *Id.*

The Examiner further contends that "[w]ith regard to the recited limitation in instant claims 3 and 28, the said limitation is not a test step. Although the art reference does not explicitly disclose 'wherein the tracer peptide displaces at least 90% of the template peptide in a parallel competition assay conducted in the absence of the first competitor peptide,' the art reference discloses that there is peptide exchange and measurement of radioactively labeled tracer peptide and also discloses that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences." *Id.*

By the foregoing amendments, claims 3, 11, 27-31, 34, 36, 45-47, 50, 81, and 86 have been cancelled. Hence, these rejections have been rendered moot as they may have applied to the cancelled claims. Applicants respectfully traverse the rejections as they may apply to the remaining claims.

As set forth above, Rothbard, in combination with Hildebrand, does not disclose the method of independent claim 85. Therefore, it follows that Rothbard and Hildebrand, in combination, do not disclose the method of claims that are dependent on claim 85.

In view of the aforementioned arguments, Applicants submit that the Examiner fails to establish a *prima facie* case of obviousness. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

Claims 13, 14, 38, 74-77, 80, 82-84, and 87 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 92/07952 A1 in view of US 2003/0191286 A1 ("the combined references") as applied to claims 2-6, 9, 11, 20-22, 25, 27-31, 34, 36, 45-47, 50, 79, 81, 85, and 86 above, and further in view of Mitchell *et al.* (Cancer Research 2000, 60: 6448-6456) (hereinafter, "Mitchell"), US 2004/0214995 A1 and US 2002/0106708 A1. By the foregoing amendments, claims 38, 74-77, 82-84, and 87 have been cancelled. Hence, this rejection has been rendered moot as it may have applied to the cancelled claims. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

The Examiner states "[t]he combined references do not disclose wherein the monomer is HLA-A2/MART-$1_{26-35}$ (claims 13 and 38), nor wherein the tracer peptide is HBc 18-27 (claim 14), nor wherein the HLA-A2 monomer is that produced in *E. coli* (claims 80, 82 and 84) . . ." Office Action at page 8.

The Examiner further states that "Mitchell *et al* teaches use of the HBc 18-27 peptide labeled with a detectable label and competing unlabeled putative epitope peptides for binding to HLA-A2." *Id.*

The Examiner also states that "US 2004/0214995 A1 discloses the low affinity peptide MART-$1_{26-35}$ that binds to HLA-A2 ([0224]), and also discloses the production of proteins in *E. coli*." *Id.*

The Examiner contends that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MART-$1_{26-35}$ peptide as the template MHC binding peptide bound to HLA-A2 in the method taught by the combined references, to have used an HLA-A2 monomer that was produced in *E. coli* . . ." *Id* at page 9. Applicants respectfully disagree with the Examiner's contentions.

As set forth above, Rothbard and Hildebrand, in combination, do not disclose the method of independent claim 85. Applicants assert that the deficiencies of Rothbard and Hildebrand are not overcome by any of the other cited references. Thus, Applicants submit that the method of the claimed invention is not disclosed by Rothbard and Hildebrand in combination of any of the other cited references. Therefore, it follows that Rothbard and Hildebrand in combination of any of the other cited references do not disclose the method of claims that are dependent on claim 85.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.

## *Conclusion*

All of the stated grounds of objections and rejections have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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